*J. Physiol.* (1982), **332**, *pp.* 427–439
*With 4 text-figures*
*Printed in Great Britain*



# LOCAL VASOACTIVITY OF OXYGEN AND CARBON DIOXIDE IN THE RIGHT CORONARY CIRCULATION OF THE DOG AND PIG

BY STEPHEN W. ELY, DONALD C. SAWYER*
AND THE LATE JERRY B. SCOTT

*From the Department of Physiology and Small Animal Surgery and Medicine, Michigan State University, East Lansing, MI 48824, U.S.A.*

(*Received 6 November 1981*)

## SUMMARY

1. Eight mongrel dogs were anaesthetized with sodium thiamylal and chloralose–urethane, ventilated, vagotomized and heparinized. Five Poland–China pigs were anaesthetized with sodium thiamylal and nitrous oxide, ventilated, vagotomized and heparinized.

2. Extracorporeal perfusion of the right coronary artery at constant pressure (100 mmHg) was instituted. A lung from a donor animal was interposed in the coronary perfusion circuit to effect changes in $CO_2$ and $O_2$ tensions in the coronary arterial blood while systemic blood gases were maintained at normal levels.

3. Local hypoxia ($P_{O_2}$ range 17–22 mmHg) produced a 25–75% decrease in coronary vascular resistance ($P < 0.05$) and a 0–24% (not significant) decrease in right ventricular $dP/dt$.

4. Local changes in $P_{CO_2}$ over the range 8–105 mmHg were associated with a 17–58% decrease in coronary vascular resistance ($P < 0.05$), a 19–24% decrease in right ventricular $dP/dt$ ($P < 0.05$) with no change in right ventricular end-diastolic pressure, and a 1–18% (not significant) decrease in heart rate.

5. These studies suggest that local decreases in $O_2$ or increases in $CO_2$ tensions produce decreases in right coronary vascular resistance that are in the opposite direction to those that would be expected from the observed changes in heart rate and contractility (two primary determinants of myocardial oxygen consumption).

6. These data support the hypothesis that $CO_2$ and $O_2$ are locally vasoactive in the coronary circulation.

## INTRODUCTION

The roles of oxygen and carbon dioxide in the regulation of coronary vascular resistance have been examined by many investigators (Hilton & Eichholtz, 1925; Gremels & Starling, 1926; Berne, 1964; Daugherty, Scott, Dabney & Haddy, 1967; Kittle, Aoki & Brown, 1965; Neil & Hattenhauer, 1975; Vance, Brown & Smith, 1973; Vance, Smith, Brown & Thorburn, 1979; Case & Greenberg, 1976). However, the importance of $CO_2$ in coronary blood flow regulation, particularly its role in functional hyperaemia has recently been challenged (van den Bos, Drake & Noble, 1979; Rooke & Sparks, 1980).

* To whom reprint requests should be sent.

Previous studies regarding the role of $CO_2$ as a coronary vasodilator were conducted using constant-flow coronary perfusion, which serves to maintain tissue $P_{O_2}$ relatively constant (Case & Greenberg, 1976; Case, Felix, Wachter, Kyrigkidis & Castellana, 1978). As a result, the negative feed-back that would occur with natural flow conditions (increased blood flow, elevated tissue $P_{O_2}$ resulting in vasoconstriction) is prevented and the vasodilatory action of $CO_2$ is unmasked. Therefore, it can be argued that opening the autoregulatory negative feed-back loop (via constant flow perfusion) may attribute a greater vasodilator potency to $CO_2$ than would be found under conditions of natural flow perfusion.

Recent studies have examined the effects of systemic alterations in arterial $P_{CO_2}$ on left coronary blood flow under natural flow (constant pressure) conditions, both with and without adrenergic blockade (van den Bos *et al.* 1979; Rooke & Sparks, 1980; Ehrhart & Smith, 1980). These data are in direct conflict with previous studies in that they can only attribute a small vasodilator capability to $CO_2$, and do not support a role for $CO_2$ in the metabolic regulation of coronary blood flow (Drake, Noble & Sparks, 1981).

The present study was conducted to address this current controversy by assessing the effect of local changes in coronary arterial $CO_2$ and $O_2$ tensions during constant-pressure perfusion of the right coronary circulation of the dog and pig. The right coronary vascular bed was chosen in that it affords several advantages over the left. It has a relatively low rate of resting $O_2$ consumption (4–5 ml. $O_2$/min per 100 g), a high flow/metabolism ratio, and a high venous $O_2$ content and $P_{O_2}$ (Ely, Sawyer, Anderson & Scott, 1981). These conditions serve to negate the complicating issues of large changes in myocardial $O_2$ consumption and tissue $P_{O_2}$ in relation to the coronary response to changes in $P_{CO_2}$. With natural flow conditions, it was felt that a better understanding of the local coronary vascular effect of $CO_2$ (or $H^+$) could be obtained.

## METHODS

Eight mongrel dogs of both sexes, weighing 25–35 kg were anaesthetized with a mixture of $\alpha$-chloralose (100 mg/kg) and urethane (500 mg/kg) given intravenously. Additional doses of chloralose were given as needed to maintain an adequate level of anaesthesia. Five Poland–China pigs (30–40 kg) were anaesthetized with sodium thiamylal (5 mg/lb., I.V.) and maintained with nitrous oxide and supplemental doses of sodium thiamylal. The animals were intubated and ventilated by a positive-pressure respirator (Harvard model 613) on room air with supplemental oxygen, at a 5 cm $H_2O$ end-expiratory pressure. Volume and rate of ventilation were adjusted to maintain arterial $P_{O_2}$, $P_{CO_2}$ and pH within the normal physiological range. Intravenous infusions of sodium bicarbonate (150 mM) were utilized when needed to counteract the metabolic acidosis associated with chloralose anaesthesia (Arfors, Arturson & Malmberg 1971). Blood anticoagulation was achieved by the intravenous administration of sodium heparin (600 u./kg, plus 250 u./kg per hr, I.V.). Oesophageal temperature was monitored (Yellow Springs) and maintained at 37 °C with a heating pad. All blood pressures were continuously monitored with Statham (low-volume displacement) pressure transducers and recorded via inputs into a direct writing oscillograph (Hewlett–Packard). Lead II of the e.c.g. was monitored for determination of heart rate and detection of arrhythmias.

The surgical preparation used is shown in Fig. 1. The left femoral artery and vein were cannulated (PE 240) for monitoring arterial pressure and intravenous infusions, respectively. The vagus nerves were isolated and sectioned bilaterally. The chest was opened by median sternotomy and the pericardium incised and sutured to the inside of the chest wall to form a cradle. A USCI

ventriculotomy catheter was passed through a purse-string suture in the right atrial appendage into the right ventricular chamber for measurement of right ventricular pressure and its first derivative, $dP/dt$. This recording system had a frequency response flat to 40 Hz. The proximal 1–3 cm of the right coronary artery was isolated in preparation for cannulation. An extracorporeal coronary perfusion system was constructed by withdrawing venous blood from the cannulated femoral vein and pumping it (Masterflex roller pump) into the pulmonary artery of an isolated lung obtained from a small donor dog or pig. Pulmonary venous blood flowed into a large bore cannula tied into the preserved left atrium of the isolated lung, passed through a water bath heated at 39 °C

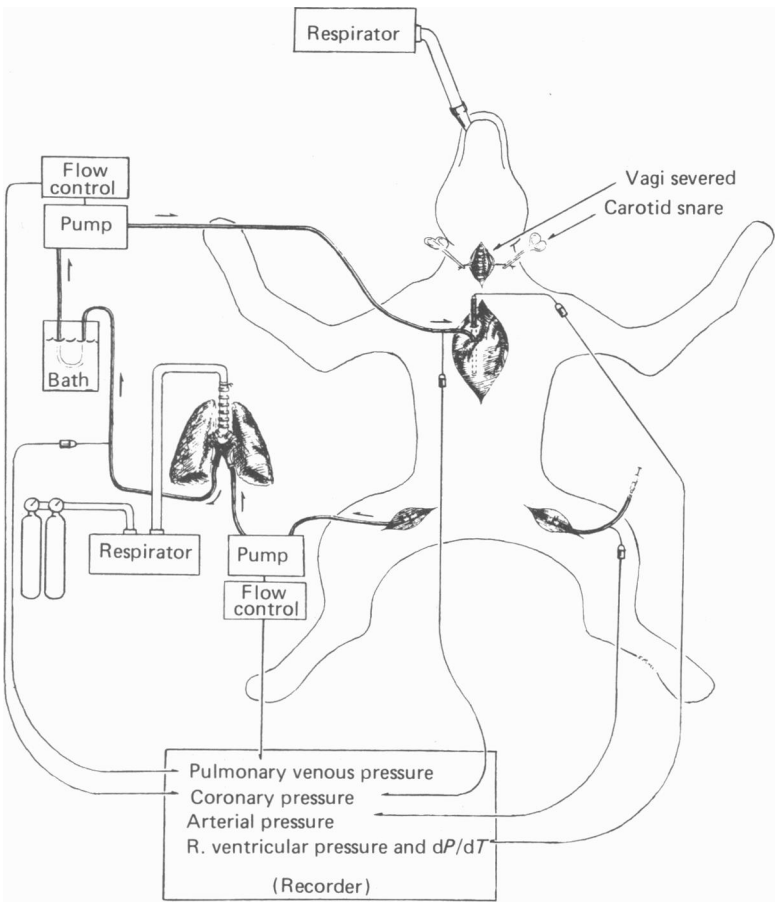


Fig. 1. Preparation for constant-pressure or constant-flow perfusion of the right coronary artery with isolated donor lung interposed in perfusion circuit. See text for further description.

and was delivered (Holter roller pump) at constant pressure (100 mmHg) to the cannulated right coronary artery. Pulmonary venous pressure in the isolated lung was monitored from a catheter in the left atrium and maintained at 5 mmHg with the use of a feed-back controller system (Leeds–Northrup) which controlled the speed of the pulmonary arterial inflow pump. The extracorporeal perfusion circuit was primed with cross-matched blood obtained from the donor lung animals, and the coronary cannula (PE240) was placed in the dissected proximal segment of the right coronary artery and was secured with silk ligatures. Coronary perfusion pressure was monitored from the coronary cannula just proximal (3 cm) to its entry into the vessel, and held constant (constant-pressure perfusion) by a second feed-back control system. The pressure drop across the last 3 cm of the cannula was determined in each experiment and was found to be $< 5$ mmHg

at maximal flow rates. Coronary blood flow was determined from the coronary pump speed which was recorded continuously on an oscillograph. The cyclic variations seen in the coronary blood-flow recordings represent oscillations in the servo-feed-back controller system. At the end of each experiment, the pump was calibrated by timed collections of blood and there was a linear relationship of pump speed to pump flow over the range of flows encountered. Crystal Violet dye (Sigma), dissolved in ethanol and saline was infused into the perfusion circuit at pressures up to 180 mmHg in the beating and fibrillating heart at the conclusion of each experiment to stain the area of the myocardium perfused. No staining occurred in the tissue perfused by the left coronary artery, suggesting a collateral-free vascular bed. The tissue was excised and the wet weight determined in order to normalize blood flows in terms of ml./min per 100 g.

To test further the possibility of the left anterior descending coronary artery or left circumflex coronary artery contributing significant collateral flow to the right coronary vascular bed, the perfusion pump was stopped and base-line perfusion pressure recorded. A fall in perfusion pressure to 15 mmHg or less indicated a relatively collateral-free preparation. The pig was also used in these studies since the right coronary circulation in the pig supplies approximately 50% of the total myocardium whereas it supplies only 15% of the total myocardium in the dog. In addition to being right-coronary dominant, the pig is similar to man in that the heart has a paucity of native collaterals.

Ventilation of the isolated perfused lung with various gas mixtures produced changes in blood–gas tensions of the coronary perfusate. Normoxia (control) was produced with 20% $O_2$, 5% $CO_2$ and 95% $N_2$. Hypocapnia was achieved by hyperventilation of the isolated lung on room air. Hypercapnia was accomplished by ventilating with 20% $O_2$, 15% $CO_2$ and 65% $N_2$. The use of the extracorporeal lung permitted rapid changes in local blood-gas tensions without producing detectable changes in systemic blood-gas tensions. Coronary arterial and systemic blood gases were measured on a radiometer blood gas analyser (Radiometer, Copenhagen). Due to the complexity of these experiments and technical difficulty in obtaining coronary venous blood samples, we were unable to obtain venous blood gas tensions or values for myocardial $O_2$ consumptions.

Indomethacin (125 mg) or Aspirin (325 mg) in isotonic saline was infused into the donor lung animal 30 min before death in order to block the synthesis of prostaglandins by the lung tissue, and therefore eliminate the possibility of prostaglandins released from the isolated lung being involved in the coronary response to alterations in blood gases.

Each experimental manoeuvre lasted approximately 10 min and was terminated when coronary arterial blood-gas tensions, and coronary blood flow or perfusion pressure had reached a steady state. Approximately 15 min was allowed for complete recovery from each experimental intervention. The order of interventions was randomized between experiments.

Control values were obtained from the period immediately preceding each experimental manoeuvre. The statistical significance of differences observed between control and experimental values were evaluated with a two-tailed, paired $t$ test (d.f. $= n-1$, for $n$ animals). A $P$ value of less than 0·05 was considered significant.

## RESULTS

### *Constant-pressure coronary perfusion in the dog*

The effects of local hypoxia, hypercapnia and hypocapnia are shown in Table 1. Coronary perfusion pressure was held constant at 100 mmHg. Local hypoxia had no effect on heart rate, arterial blood pressure, right ventricular systolic pressure or $dP/dt$. Hypoxia produced a substantial coronary effect as evidenced by the 263% increase in coronary blood flow and 74% decrease in coronary vascular resistance (mean coronary perfusion pressure/mean coronary blood flow). Fig. 2 is a representative tracing obtained from one animal, depicting the response to local hypoxia. In this series, coronary arterial $P_{O_2}$ was decreased from 144 to 17 mmHg while $P_{CO_2}$ and pH remained unchanged. During hypercapnic perfusion ($P_{CO_2} = 105$ mmHg, pH = 7·05), coronary blood flow increased 98% and resistance decreased by 47%. Heart rate and arterial blood pressure were unaffected by hypercapnia; however right

TABLE 1. Effects of changes in coronary $P_{O_2}$ and $P_{CO_2}$ during constant-pressure perfusion in the dog

| | Hypoxia ($n = 8$) | | Hypercapnia ($n = 7$) | | Hypocapnia ($n = 7$) | |
|---|---|---|---|---|---|---|
| | C | E | C | E | C | E |
| Heart rate (beats/min.) | 157±9 | 156±9 | 155±8 | 142±11 | 157±9 | 175±9* |
| Mean arterial blood pressure (mmHg) | 83±9 | 77±8 | 92±10 | 85±10 | 94±10 | 85±10* |
| RV systolic pressure (mmHg) | 23±1 | 24±2 | 25±2 | 23±1 | 26±2 | 24±2* |
| RV $dP/dt$ (mmHg/sec) | 1531±505 | 1523±625 | 1707±420 | 1357±304* | 1721±482 | 1800±561 |
| RCA blood flow (ml./min per 100 gm) | 57·6±6·1 | 211·3±11·6* | 67·1±3·9 | 133±12·5* | 63·2±4·0 | 55·3±9·1 |
| Coronary vascular resistance (mmHg/ml. per min per 100 g) | 1·89±0·19 | 0·48±0·02* | 1·53±0·09 | 0·81±0·07* | 1·62±0·18 | 1·96±0·34 |
| Coronary arterial pH | 7·36±0·02 | 7·30±0·03 | 7·36±0·02 | 7·05±0·04* | 7·36±0·02 | 7·74±0·05* |
| Coronary arterial $P_{CO_2}$ (mmHg) | 46±1 | 49±2 | 46±1 | 105±11* | 46±1 | 8±1* |
| Coronary arterial $P_{O_2}$ (mmHg) | 144±2 | 17±1* | 144±2 | 145±13 | 144±2 | 146±10 |

Results are expressed as mean ±S.E. of mean.
Coronary perfusion pressure held constant at 100 mmHg.
*, significantly different from control at $P < 0·05$.
C, control; E, experimental; RV, right ventricular; RCA, right coronary artery.

ventricular $dP/dt$ was significantly decreased (20%). Fig. 3 is a representative tracing which shows the coronary response to an acute local increase in coronary arterial $CO_2$.

Hypocapnic perfusion ($P_{CO_2}$, 8 mmHg; pH, 7·74) produced a slight increase in heart rate and a slight decrease in arterial blood pressure and right ventricular systolic pressure. No change was detected in $dP/dt$. Coronary blood flow was decreased by 12% and coronary vascular resistance was increased by 20%. While these changes

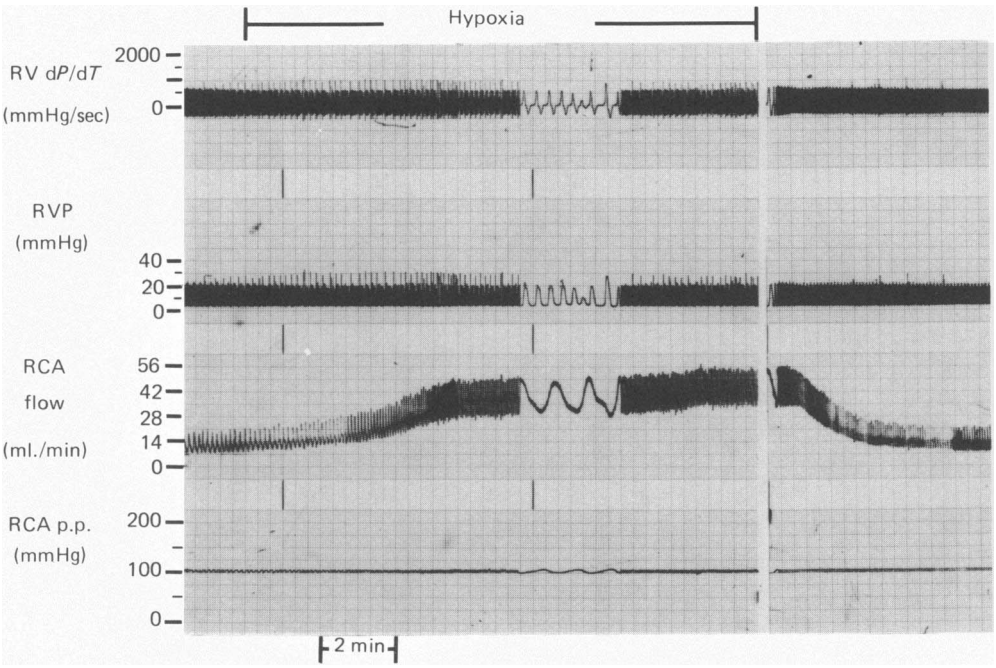


Fig. 2. A representative tracing from one animal showing the effect of lowering right coronary arterial $P_{O_2}$ from 144 to 17 mmHg on right ventricular pressure (RVP), right ventricular $dP/dt$, right coronary artery blood flow with coronary perfusion pressure (RCA p.p.) held constant at 100 mmHg. Heart rate and mean arterial blood pressure (not shown) were unchanged.

were not statistically significant, coronary vascular resistance increased in six out of seven animals studied. Fig. 4 is a representative tracing showing the response to local hypocapnia. In this animal, a transient increase in coronary blood flow was followed by a sustained decrease in flow.

*Constant-pressure coronary perfusion in the pig*

The effects of changes in right coronary artery blood $P_{O_2}$ and $P_{CO_2}$ in the pig are shown in Table 2. Coronary perfusion pressure was held constant at 120 mmHg. Hypoxic perfusion ($P_{O_2}$ decreased from 84 to 22 mmHg) had no effect on heart rate or arterial blood pressure. Right ventricular systolic pressure and $dP/dt$ were decreased by 8 and 24% respectively. These changes were not significant, perhaps due to the small number of animals studied. Hypoxia produced a 27% increase in coronary blood flow with an associated decrease in coronary vascular resistance.

TABLE 2. Effects of changes in coronary $P_{O_2}$ and $P_{CO_2}$ during constant-pressure perfusion in the pig

| | Hypoxia ($n = 3$) | | Hypercapnia ($n = 3$) | | Hypocapnia ($n = 4$) | |
|---|---|---|---|---|---|---|
| | C | E | C | E | C | E |
| Heart rate (beats/min.) | 156±13 | 163±17 | 155±16 | 152±13 | 155±13 | 161±14 |
| Mean arterial blood pressure (mmHg) | 88±6 | 85±2 | 90±4 | 87±6 | 92±4 | 90±5 |
| Right ventricular systolic pressure (mmHg) | 35±3 | 32±2 | 34±1 | 32±1* | 32±1 | 30±1 |
| Right ventricular $dP/dt$ (mmHg/sec.) | 1333±83 | 1000±0 | 1160±65 | 940±79* | 1125±125 | 1000±102 |
| RCA blood flow (ml./min per 100 g) | 84±32 | 107±36* | 94±26 | 118±36* | 74±8 | 63±20 |
| Coronary vascular resistance (mmHg/ml. per min per 100 g) | 1·80±0·58 | 1·33±0·37 | 1·57±0·029 | 1·30±0·26* | 1·68±0·25 | 5·10±3·57 |
| Coronary arterial pH | 7·37±0·02 | 7·37±0·06 | 7·40±0·02 | 7·24±0·01* | 7·40±0·03 | 7·81±0·03* |
| Coronary arterial $P_{CO_2}$ (mmHg) | 36±1 | 37±2 | 37±2 | 68±3* | 44±3 | 10±1* |
| Coronary arterial $P_{O_2}$ (mmHg) | 84±3 | 22±1* | 117±16 | 116±19 | 109±20 | 130±16 |

Results are expressed as mean ±S.E. of mean.
Coronary perfusion pressure held constant at 120 mmHg.
*, significantly different from control at $P < 0·05$.
C, control; E, experimental; RCA, right coronary artery.

Hypercapnic perfusion ($P_{CO_2}$, 68 mmHg; pH, 7·24) had no effect on heart rate or arterial blood pressure; however right ventricular systolic pressure and d$P$/d$t$ was decreased by 5 and 19 % respectively. Coronary blood flow was increased by 25 % and coronary resistance was decreased by 17 %.

Hypocapnic perfusion ($P_{CO_2}$, 10 mmHg; pH, 7·81) had no effect on heart rate, arterial blood pressure, right ventricular pressure or d$P$/$dt$. Coronary blood flow was not changed significantly; however during hypocapnia perfusion blood flow decreased in three of the four animals studied, and in one animal it decreased 85 % from 56 to 8 ml./min per 100 g.

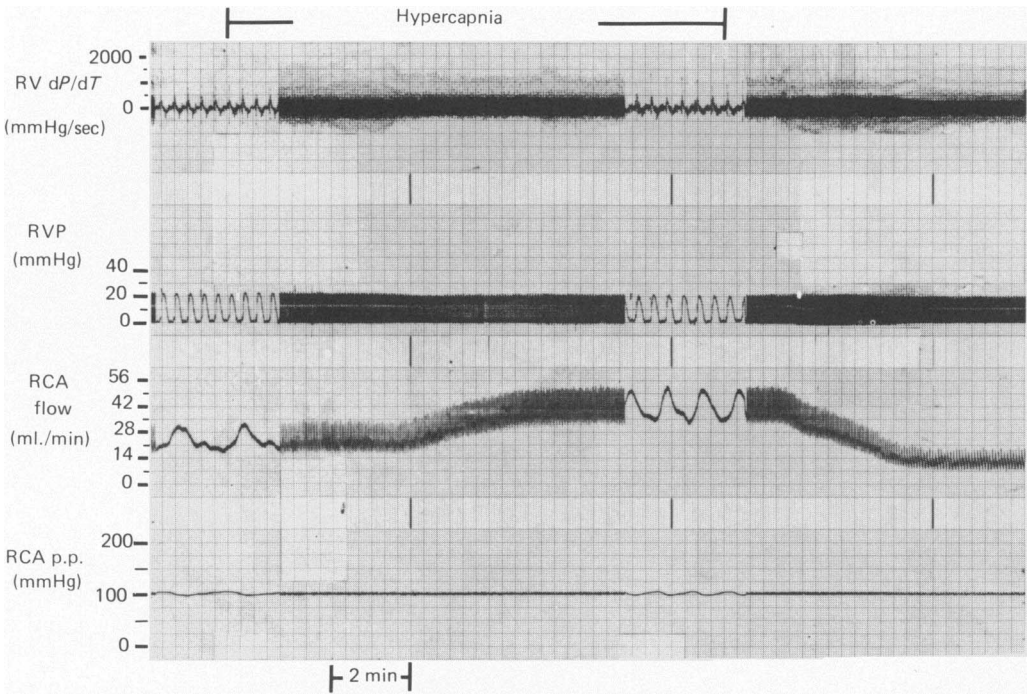


Fig. 3. A representative tracing from one animal showing the effect of increasing right coronary arterial $P_{CO_2}$ from 45 to 100 mmHg on right ventricular pressure (RVP), and right coronary blood flow with coronary perfusion pressure (RCA p.p.) held constant at 100 mmHg. Heart rate and mean arterial blood pressure were unchanged.

## DISCUSSION

The decrease in right coronary resistance that follows hypoxic and hypercapnic perfusion, and the increase in resistance that follows hypocapnic perfusion probably result from changes in the activity of vascular smooth muscle. Extraluminal pressure has been shown to have little influence on right coronary artery resistance (Bellamy & Lowensohn, 1980; Gregg, 1937), and intraluminal pressure was maintained constant at 100 mmHg; arterial haematocrit (and therefore blood viscosity) was also constant.

*Oxygen*

These studies demonstrate that under constant pressure perfusion in the dog and pig, a marked reduction in coronary arterial $P_{O_2}$ from 144 to 20 mm Hg results in a 25–75% decrease in coronary vascular resistance. Thus, these data are consistent with the pre-existing evidence that hypoxia is a potent vasodilator in the left coronary circulation (Berne, Blackmon & Gardner, 1957; Case & Greenberg, 1976; Green & Wegria, 1941, Markwalder & Starling, 1913). It is unclear whether the vasoactivity associated with low oxygen tensions is a direct effect on vascular smooth muscle or

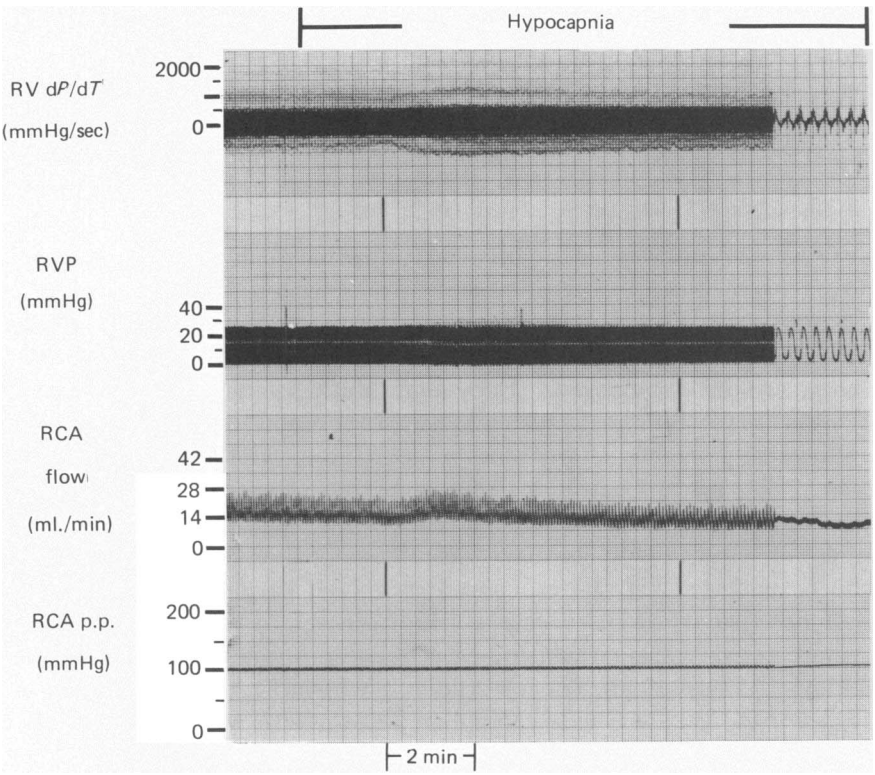


Fig. 4. A representative tracing from one animal showing the effect of local hypocapnia ($P_{CO_2}$ 45–8 mmHg) on right ventricular pressure (RVP), and right coronary blood flow with coronary perfusion pressure held constant at 100 mmHg. Heart rate increased (160–170 beats/min) while mean arterial pressure decreased (120–115 mmHg).

an indirect effect mediated through the release of vasodilator metabolites from myocardial cells.

Although the present study does not directly shed light on the mechanism of hypoxic dilation, it does lead to an interesting speculation. Since the right ventricle performs less work (one sixth) and may generate less wall tension than the left heart, it also consumes less oxygen. In this regard, recent studies in our laboratory have shown that resting right ventricular myocardial oxygen consumption as well as right coronary arterio–venous oxygen difference are substantially less than the values

reported for the left heart. Consequently, the response to local alterations in coronary arterial $P_{O_2}$ and $P_{CO_2}$ may largely represent the direct action of the stimulus on the vascular smooth muscle, since metabolic influences represent a relatively minimal contribution to vascular control in this vascular bed.

The local vasoactivity of $O_2$ in the intact dog during constant flow left coronary perfusion was demonstrated by Daugherty *et al.* 1967). These investigators reported that the perfusate oxygen tension had to be decreased below 40 mmHg before a fall in coronary resistance and left ventricular contractile force could be detected. In the present study, lowering coronary $P_{O_2}$ in the dog to 12–17 mmHg produced a substantial coronary vasodilation; however right ventricular pressure and $dP/dt$ were unaffected. This may be due to the fact that a portion of the right ventricular free wall and interventricular septum are perfused by branches from the left coronary artery. Our physiological data as well as microsphere data confirm the latter conclusion (Murray, Baig & Vatner, 1980). Therefore, only a portion of the total right ventrical was perfused with hypoxic blood via the right coronary artery.

*Carbon dioxide*

There are several reports by other investigators which suggest that an increase in systemic $CO_2$ tension causes a decrease in left coronary vascular resistance (Feinberg, Gerola & Katz, 1960; Hilton & Eichholtz, 1925; Kittle *et al.* 1965; Ledingham, McBride, Parratt & Vance, 1970, Markwalder & Starling, 1913, Vance *et al.* 1979) although there are dissenting views (Eckenhoff, Hafkenschiel & Landmesser, 1947, Green & Wegria, 1941). Similarly, systemic hypocapnia induced by hyperventilation has been shown to decrease left coronary blood flow (Kittle *et al.* 1965, Neill & Hattenhauer, 1975; Rowe, Castillo & Crumpton, 1962; Vance *et al.* 1973). However, the interpretation of studies in which systemic $CO_2$ tension is altered is difficult, in that the direct effect of $CO_2$ on coronary vascular smooth muscle may be masked by indirect effects mediated via altered concentrations of various plasma constituents including Angiotensin II, ADH and potassium, as well as an altered sympathetic nervous system activity and circulating catecholamines (Schribner, Fremont-Smith & Burnell, 1955; Tenney, 1956). The few studies in which $CO_2$ tension has been altered locally suggest that $CO_2$ has a mild (Daugherty *et al.* 1967) to dramatic effect (Case & Greenberg, 1976; Case *et al.* 1978) on left coronary vascular resistance when this vascular bed is perfused at constant flow. Data from the latter studies suggest that variations in coronary arterial $P_{CO_2}$ can alter left coronary vascular resistance over the entire range from maximal constriction to maximal dilation. Local changes in $CO_2$ tensions have not been evaluated during constant pressure perfusion, a condition closer to that under natural flow conditions.

Van den Bos *et al.* (1979), Rooke & Sparks (1980) and Ehrhart & Smith (1980) have examined the effects of systemic alterations in $P_{CO_2}$ and measured left coronary blood flow under natural flow conditions. The net conclusion of these three recent studies is as follows.

(1) Changes in systemic arterial levels of $CO_2$ do produce changes in left coronary vascular conductance, but these changes are prevented with adrenergic blockade. Systemic changes in $CO_2$ have indirect effects via activation of the sympathetic nervous system (van den Bos *et al.* 1979; Ehrhart & Smith, 1980). In the presence

of adrenergic blockade, $CO_2$ has only a minimal effect on coronary vascular resistance (van den Bos *et al.* 1979).

(2) Elevations of arterial $CO_2$ produces a shift in the oxyhaemoglobin dissociation curve, yielding a higher $P_{O_2}$ for a given $O_2$ content. This produces a resultant rise in venous (and probably tissue) $P_{O_2}$, which in turn results in vasoconstriction, thereby masking any $CO_2$-induced vasodilation (van den Bos *et al.* 1979; Rooke & Sparks, 1980).

(3) During natural flow conditions, elevation of systemic arterial $P_{CO_2}$ results in a small increase in coronary blood flow for any given level of oxygen consumption. This, in addition to the fact that coronary sinus $P_{CO_2}$ does not increase appreciably with increased levels of myocardial $O_2$ consumption suggests that $CO_2$ is a weak coronary vasodilator and could not be regarded as an important factor in the metabolic regulation of coronary blood flow (Rooke & Sparks, 1980).

The current study utilized local changes in coronary arterial $CO_2$ tensions to avoid the systemic reflex sympathetic response which occurs with systemic alterations in blood gases, and constant-pressure perfusion to simulate a more physiological condition. The effects of $CO_2$ were examined in the right coronary vascular bed, which has been shown to be a bed which is much less dominated by metabolic factors than its left counterpart (Ely *et al.* 1981).

The present data demonstrate that changes in coronary arterial $P_{CO_2}$ with associated changes in pH produce substantial alterations in right coronary vascular resistance. Since right ventricular end-diastolic pressure was unchanged, the decrease in $dP/dt$ probably resulted from a fall in right ventricular contractility. Thus, heart rate and contractility, two important determinants of myocardial oxygen consumption, were decreased when going from a hypo- to a hypercapnic state. The fact that coronary vascular resistance was decreased at a time when myocardial oxygen consumption was most likely decreased suggests that the vascular response is the result of a direct effect of $CO_2$ (or $H^+$ ion) on the coronary vasculature. This would suggest that $CO_2$ is capable of acting as an important coronary vasodilator if local $CO_2$ levels were elevated sufficiently.

We disagree, on the basis of our data, with the contention that $CO_2$ is a weak coronary vasodilator (Rooke & Sparks, 1980), and point out that vascular effects that accompany systemic alteration in gas tensions are difficult to interpret because such interventions produce changes in the plasma levels of several vasoactive hormones as well as activity of the autonomic nervous system (van den Bos *et al.* 1979; Ehrhart & Smith, 1980). Furthermore, coronary venous determinations of $P_{CO_2}$ cannot serve as an accurate index of interstitial $CO_2$ at all levels and regions of the myocardium. Therefore, these measurements would not necessarily reflect $CO_2$ tensions in certain regions of the myocardium where local $CO_2$ may rise to vasoactive levels. Hillis, Khuri, Braunwald, Kloner, Tow, Barsamian & Maroko, (1979) reported that local intramyocardial $P_{CO_2}$ (as measured with a mass spectrometric technique) increased to approximately 130 mmHg with coronary artery occlusion. Therefore there may be many situations in which local $P_{CO_2}$ tensions increase to levels substantially above normal, and data from the present study demonstrate that these levels are capable of producing substantial coronary vasodilation.

We gratefully acknowledge the technical assistance of Don Anderson, C. Kitazumi, R. Korthuis and W. Stoffs. Special thanks are due to Linda Friedsberg for the preparation of this manuscript. This work was supported by grants from the National Heart, Lung and Blood Institute (HL 10879-11A1) and the Michigan Heart Association.

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